Contralateral medial temporal lobe damage in right but not left temporal lobe epilepsy: a ^1H magnetic resonance spectroscopy study

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Background: Proton magnetic resonance spectroscopy (MRS) of the hippocampus is useful in lateralising the epileptic focus in temporal lobe epilepsy for subsequent surgical resection. Previous studies have reported abnormal contralateral MRS values in up to 50% of the patients.

Objective: To identify the contributing factors to contralateral damage, as determined by MRS, and its extension in patients with temporal lobe epilepsy.

Methods: Single voxel MRS was carried out in the hippocampus and lateral temporal neocortex of both hemispheres in 13 patients with left temporal lobe epilepsy (LTLE) and 16 patients with right temporal lobe epilepsy (RTLE). All patients had mesial temporal lobe epilepsy with hippocampal sclerosis. Controls were 21 healthy volunteers of comparable age.

Results: Consistent with previous studies, the NAA/(Cho+Cr) ratio was abnormally low in the hippocampus ipsilateral to the focus ($p < 0.0001$), and there were lower values in both patient groups in the ipsilateral temporal neocortex ($p < 0.0001$). Patients with RTLE had left hippocampal MRS anomalies ($p = 0.0018$), whereas the right hippocampus seemed to be undamaged in LTLE patients.

Conclusions: Unilateral mesial temporal lobe epilepsy is associated with widespread metabolic abnormalities which involve contralateral mesial and neocortical temporal lobe structures. These abnormalities appear to be more pronounced in patients with RTLE.

Proton magnetic resonance spectroscopy (MRS) techniques have been used successfully over the last 10 to 15 years to confirm lateralisation in patients with evidence of lesional^{1–5} and non-lesional⁶ temporal lobe epilepsy. The principal signals of interest have been those from N-acetylaspartate and from creatine+phosphocreatine and choline containing compounds. Studies have shown that N-acetylaspartate reflects neuronal function or density, whereas choline and creatine concentrations correlate with glial cell density.^{7,8} Thus decreased N-acetylaspartate is considered to indicate neuronal loss or dysfunction, whereas increased choline and creatine suggest gliotic changes. Both conditions are present in hippocampal sclerosis. In addition, measurements of N-acetylaspartate, creatine, and choline can detect subtle tissue alterations and are consequently useful in the non-invasive localisation and lateralisation of the epileptic focus. Correct lateralisation to the side of seizure onset was found in 55% to 100% in patients with positive magnetic resonance imaging (MRI) findings or successful temporal lobe resection.^{1–3,9–11} Interestingly, up to 50% of the patients also had abnormalities in the contralateral temporal lobe, both in adults and children.^{9–11} However, factors contributing to the contralateral damage are as yet unclear.

One possible contributing factor is the side of seizure origin. There is some evidence that patients with left and right temporal foci differ with respect to several clinical variables. In a previous study we found worse psychosocial functioning in patients with right temporal foci.¹² In the same patient group, altered contralateral hippocampal volumes were noted in those with right but not left temporal lobe epilepsy, as determined by volumetric analysis. Postoperative examination of the patients revealed that the group with left sided temporal resections showed progressive impairment of verbal memory, whereas the group with right sided resections had better recovery or less memory loss preoperatively.^{13,14} In another study, patients with right mesial temporal lobe epilepsy also

showed verbal memory impairment, indicating bilateral functional impairment, as compared with patients with left mesial temporal lobe epilepsy.¹⁵ Taking these observations together, the right temporal lobe seems to act more bilaterally than the left, either in terms of recruitment of contralateral resources or in terms of affecting contralateral structures.

Our aim in the present study was to determine whether these differential (dys)functional patterns were reflected in contralateral metabolic changes, and if so, which structure—hippocampal or neocortical temporal—was secondarily affected.

METHODS

Subjects

Our study group consisted of 29 consecutive patients with temporal lobe epilepsy, referred to our laboratory for evaluation for surgical treatment. To minimise possible variations resulting from different histopathological findings, we only studied patients with temporal lobe epilepsy associated with unilateral hippocampal atrophy. The assessment of the patients included continuous video EEG monitoring, structural high resolution MRI, positron emission tomography (PET), and neurological and neuropsychological examination. Clear localisation of the focus was achieved in all cases. Thirteen patients had left temporal lobe epilepsy (LTLE) and 16 had right temporal lobe epilepsy (RTLE). In six patients (three LTLE, three RTLE), contralateral EEG anomalies were noted; their frequency was calculated to be $< 30\%$. The volume loss was confirmed in all cases by volumetric measurements.

The mean (SD) age of the patients was 32.8 (11.8) years, age of onset 11.1 (8.4) years, and duration of epilepsy 21.8 (12.7) years (table 1). Although the RTLE patients tended to have a greater seizure frequency than the LTLE patients, this difference did not reach significance. Of the 29 patients, 26

Table 1 Clinical details of patients and controls

	Controls	LTLE	RTLE
n	21	13	16
Age (years)	28.9 (11.4)	32.4 (12.9)	33.2 (11.4)
Age of onset (years)	–	13.5 (10.2)	9.1 (6.3)
Duration of epilepsy (years)	–	18.9 (13.4)	24.1 (12.1)
Seizure frequency*	–	5.0 (3.2)	12.2 (13.7)

Values are mean (SD).

*Seizures/month, including complex partial and secondary generalised seizures.

LTLE, left temporal lobe epilepsy; RTLE, right temporal lobe epilepsy.

were operated on and tissue obtained was examined for histological abnormalities (three selective amygdalo-hippocampectomies, 23 partial temporal lobectomies). The diagnosis of hippocampal gliosis and sclerosis was confirmed in all cases. In the temporal neocortex, one specimen was considered normal, four showed neuronal heterotopias, and 17 revealed gliotic changes. Twenty eight of the 29 patients became seizure-free; the remaining patient had a significant reduction in seizure frequency (by more than 80%). The follow up was over a period of 4 to 74 months, mean 38.3 months.

Twenty one healthy volunteers of comparable age served as controls (table 1). There was no significant age difference between the controls and patient groups.

Magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (^1H -MRS) was undertaken on a 1.5 tesla Eclipse system (Marconi Medical Systems, Cleveland, Ohio, USA) with a standard head coil. The ^1H -MRS measurements consisted of long echo time PRESS sequences (repetition time (TR)/echo time (TE)/number of

averages (NAV): 1600 ms/270 ms/256), centred on the hippocampi (voxel volume 4.6 ml) and the temporal lobes (voxel volume 9.4 ml). Figure 1 shows the placement of the single voxel in the mesial and lateral temporal lobe. Owing to shimming issues and to avoid contamination from subcutaneous fat, the voxel of the temporal lobe was centred on the superior and middle temporal sulcus, at the mid-portion of the temporal lobe. The voxel encompassed grey and white matter with the proportion of grey matter being on average 55%.

Data reduction was done using SAGE spectroscopy analysis software (General Electric Medical Systems, Fremont, California, USA) and consisted of low frequency filtering, 4 Hz exponential apodisation, zero filling, Fourier transform, automatic zero order phase correction, and baseline correction for dc offset. The peak amplitudes were derived after fitting of the spectra using the Marquardt algorithm of the SAGE program. The metabolites assessed by this method were the choline containing compounds (Cho), the creatine and phosphocreatine (Cr), and the N-acetylaspartate (NAA). The ratio of peak amplitudes ($\text{NAA}/(\text{Cho}+\text{Cr})$) is reported.

Statistics

MRS data were collected before surgery by a magnetic resonance technologist. The analysis was carried out blinded to the results of the presurgical investigation. The intensity ratio $\text{NAA}/(\text{Cho}+\text{Cr})$ was used as an index of spectral abnormality. An analysis of variance (ANOVA) was undertaken for comparison of the measured structure (hippocampus or lateral temporal neocortex) and the side of pathology (left *v* right, or ipsilateral *v* contralateral, respectively) between all three groups (control group, LTLE, RTLE). Two tailed *t* tests were used for detailed analysis. A Pearson's correlation coefficient test was done for correlation of metabolite indices with clinical variables such as age or duration of epilepsy, or between metabolite measurements from different structures

Figure 1 Voxel placement in the lateral and mesial structures of the right temporal lobe of a volunteer.

Table 2 NAA/(Cho+Cr) measurements in both temporal lobes of the patient and control groups

	Controls	LTLE	p Value	RTLE	p Value
n	21	13		16	
Left hippocampus	0.76 (0.067)	0.60 (0.086)	0.00001	0.69 (0.073)	0.0018
Left temporal neocortex	1.12 (0.094)	0.86 (0.17)	0.00001	1.0 (0.11)	0.0015
Right hippocampus	0.75 (0.052)	0.72 (0.052)	NS	0.58 (0.088)	<0.00001
Right temporal neocortex	1.13 (0.086)	0.99 (0.091)	0.0001	0.82 (0.14)	<0.00001

Values are mean (SD); p values refer to comparison with the control group.
LTLE, left temporal lobe epilepsy; NAA, RTLE, right temporal lobe epilepsy.

within the same patients. Comparisons within the same patient group were done using dependent *t* tests. A probability (*p*) value of < 0.05 was considered significant for ANOVA and *t* tests, while a *p* value of < 0.01 was required for statistical significance in correlation comparisons.

RESULTS

Controls

The average NAA/(Cho+Cr) ratios in the hippocampal and lateral temporal neocortex are shown in table 2. No significant correlations were found either between age and hippocampal or neocortical measurements, or between left and right hippocampi or left and right temporal neocortex ratios.

Patients

Although the patients with RTLE tended to have a greater seizure frequency, the difference was not significant (*p* = 0.08). Moreover, the two groups did not differ with respect to any other clinical variable and are thus considered comparable, except for focus lateralisation.

ANOVA across all three groups, both sides, and both voxel sites revealed a highly significant group effect ($F(2,47) = 44.92$; $p < 0.0001$) because of smaller values in the patient groups. There was also a significant structure effect ($F(1,47) = 396.57$; $p < 0.0001$) owing to overall higher MRS

ratios in the temporal neocortex. A group by structure interaction also became evident ($F(2,47) = 4.96$; $p < 0.011$): not only were the hippocampal NAA/(Cho+Cr) ratios smaller than the neocortical values in all three groups, but there also seemed to be even smaller values in the RTLE group. The significant group by side interaction ($F(2,47) = 41.02$; $p < 0.0001$) was caused by diminished NAA/(Cho+Cr) ratios predominantly ipsilateral to the focus in the patient groups. The major findings were not affected by age, frequency of generalised tonic-clonic seizures, duration of epileptic disorder, or overall seizure frequency as a covariate.

With regard to the values obtained in the contralateral temporal lobe, a significant difference emerged between LTLE and RTLE. While the NAA/(Cho+Cr) ratio of the right hippocampus in the LTLE patients did not differ from the control group, the left hippocampus in the RTLE patients showed markedly smaller values ($df = 35$, $t = 3.38$, $p = 0.0018$; fig 2). With respect to the neocortical measurements, no such differential effect was noted, and in LTLE and RTLE abnormally low indices were obtained bilaterally but with the ipsilateral neocortex predominating (table 2).

Correlation analysis was done between clinical variables such as age, age of onset, duration of disease, seizure frequency, frequency of generalised tonic-clonic seizures, and NAA/(Cho+Cr) indices in the left and right hippocampus and temporal neocortex. This was carried out for both patient groups combined and for each patient group separately. We also investigated a possible effect of bilateral *v* unilateral EEG anomalies. No significant association was found. Moreover, in the patient groups, we did not observe a significant correlation between the hippocampal and neocortical NAA/(Cho+Cr) within the same temporal lobe or between homologous structures in the two temporal lobes. In particular, for the left hippocampal values in the RTLE group, no meaningful association with any other clinical or metabolic variable was noted.

DISCUSSION

In this study we were interested to explore a possible differential effect of left and right mesial temporal foci in an otherwise homogeneous patient group. Consistent with previous studies, we found a highly significant diminution of the NAA/(Cho+Cr) peak ratios in the affected ipsilateral hippocampus in patients with chronic temporal lobe epilepsy and hippocampal sclerosis compared with healthy controls. We also found major differences in the lateral temporal cortex, again supporting previous observations of extrahippocampal changes in patients with temporal lobe epilepsy.^{16–19} These changes seemed to be independent of the mesial temporal lobe abnormalities, as no correlation was found between lateral and mesial intensity ratios. In contrast to other observations,^{20, 21} we did not find any relation with the frequency of generalised tonic-clonic seizures in either patient group. As in previous reports, we were unable to show an association with total seizure frequency or with the duration of the seizure disorder.^{20, 21} Thus it appears unlikely that the neocortical changes are just a “secondary” effect of the

Figure 2 Mean ratio of N-acetylaspartate to choline plus creatine $\text{NAA}/(\text{Cho}+\text{Cr})$ from the hippocampus in the control and patient groups. Clear columns, left sided values; shaded columns, right sided values; error bars = 1 SD. Significant differences were found for both hippocampi in the RTLE group (right > left). In the LTLE group, the left hippocampus but not the right hippocampus showed smaller intensity ratios. **p* = 0.0018, ***p* < 0.001. LTLE, left temporal lobe epilepsy; RTLE, right temporal lobe epilepsy.

hippocampal focus or are related to the duration and severity of the epilepsy. Moreover, in all but one patient the histopathological analysis of the temporal neocortex revealed tissue abnormalities suggesting that the low intensity values obtained from this brain region indeed reflected structural changes.

We also found MRS abnormalities in the contralateral temporal lobe, in accordance with previous observations.^{9, 22} The significance of the abnormal values in the contralateral temporal lobe is uncertain. It has been reported that abnormal contralateral values may improve postoperatively^{23–25} and that bilateral low intensity values do not preclude a good surgical outcome,²⁶ suggesting that decreased N-acetylaspartate values or N-acetylaspartate dependent ratios reflect only functional (and possibly transient) changes.^{27, 28} However, presurgical spectra of the resected temporal lobe are also abnormally low and are associated with “real” pathological tissue, as determined by postoperative histological analysis. Thus contralaterally abnormal ratios may be an underlying cause in those patients who do not show postoperative recovery.²⁵ In a necropsy study of patients with temporal lobe epilepsy, abnormalities in both hippocampi were found in 30% of the cases,²⁹ indicating that contralateral low hippocampal and neocortical NAA/(Cho+Cr) values indeed represent tissue abnormalities, although they might not be as epileptogenic as in the resected side. In a follow up study of a patient suffering from occipital focal status epilepticus, N-acetylaspartate was lowest on day 4 after status onset, recovered partially over the next months, but remained low even after one year and despite good clinical seizure control.^{30, 31} This observation suggests that a certain quantity of N-acetylaspartate loss is reversible and thus of transient character, but that another portion of the decrease is permanent and reflects underlying damage, although not necessarily related to clinically evident seizure activity.

The differential effect on the contralateral hippocampus of a right compared with a left temporal focus, as shown by MRS, has not yet been described. Other lines of evidence, however, suggest a differential effect of a right versus left mesial temporal focus. Neuropsychological studies in patients with temporal lobe epilepsy agree that patients with LTLE more often encounter a significant postoperative verbal memory decline, whereas patients with RTLE have less or no impairment in visuo-spatial memory postoperatively,^{32–35} indicating successful recruitment of extrahippocampal or extratemporal resources in RTLE to compensate for the deficit. In the preoperative situation patients with RTLE suffered from verbal memory deficits compared with the controls, indicating additional left hippocampal dysfunction, although their performance was still better than that of LTLE patients.¹⁵

Two explanations of the differential left-right effect are possible: first, that there are established pathways between the right and left hemispheric structural changes, existing before the onset of epilepsy and unrelated to the epilepsy; and second, that the differential projection pathways are non-physiological and are related to the pathological activity in the (right) mesial temporal lobe structures (secondary epileptogenesis). The MRS data were not correlated with clinical variables such as duration of disease or seizure frequency, which would be expected if they were entirely dependent on the activity of the focus. However, normalisation of metabolic variables in the contralateral temporal lobe postoperatively lends support to the concept of secondary epileptogenesis.^{23, 24} Arguments for the first hypothesis come from paediatric studies. The normal development of the right hemisphere determines left hemispheric function to some degree: children with early right hemispheric lesions may have similar problems in their verbal skills as children with early left hemispheric lesions, who do not show the adult pattern of aphasia after acquired (unilateral) left perisylvian lesions.³⁶

These observations suggest that the right hemisphere contributes to the development of left hemispheric function.

Moreover, the right hemisphere and its functions (for example, face recognition) develop earlier than those assigned to the left hemisphere, as confirmed by a recent functional imagery study.³⁷ Putting all the findings together, the right hemisphere seems to have a “nurturing” function for the development of the left hemisphere, which suggests the presence of specialised, physiological, right to left interhemispheric propagation pathways. Our findings indicate the existence of such a pathway on the hippocampal level but not on the neocortical level.

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HISTORICAL NOTE.....

Acute childhood hemiplegia

Acute hemiplegia in childhood has many causes. Many are vascular, some follow trauma or a variety of encephalitis. Carotid and other basal vascular occlusions may result from cardiac emboli, angiomas, small vessel disease, or in some cases from an arteritis.¹ Most children who begin with prolonged focal or generalised epilepsy are left with significant motor deficits, hyperkinetic behaviour, and many with recurrent fits and cognitive defects.

Little was written about the natural history until the 1960s.^{2–3} Sigmund Freud gave a good description⁴ in 1897, which like many of his neurological studies at the Salpêtrière is commonly forgotten.^{5–6}

"A previously healthy child without hereditary predisposition suddenly became ill from a few months to 3 years of age. The aetiology of the illness remains unknown or is sought in a simultaneously occurring infectious disease. The initial symptoms may be violent, with fever, convulsions, or vomiting, or may be slight and insignificant . . . speech impediment and aphasia are frequent and usually temporary;

hemianopsia and paralysis of the eye muscles is rare . . . mental disturbance of varied degree is usually apparent. Sooner or later, after the onset of the disease, epileptic seizures occur."

Freud also here portrayed the bony hypertrophy of the frontal bone and orbits associated with the subsequent cerebral atrophy (the Dyke-Davidoff-Masson skull described in 1933).

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